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Replacement of Broad-Spectrum Cephalosporins by Piperacillin-Tazobactam: Impact on Sustained High Rates of Bacterial Resistance

Carlos Bantar,[1]* Eduardo Vesco,[2] Claudia Heft,[3] Francisco Salamone,[4] Marcelo Krayeski,[2] Hernán Gomez,[2] María Alicia Coassolo,[3] Alejandro Fiorillo,[2] Diego Franco,[1] Carina Arango,[3] Fernando Duret,[5] and María Eugenia Oliva[1]*

Committee for Prevention and Control of Nosocomial Infection,[1] and Departments of Internal Medicine,[2] Pharmacy,[3] and Microbiology,[4] Hospital San Martín, Paraná, Entre Ríos, and Wyeth-Whitehall, Buenos Aires,[5] Argentina

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We have previously observed a significant reduction of ceftriaxone resistance in *Proteus mirabilis* associated with an increase in the use of cefepime, along with a decrease in the consumption of broad-spectrum cephalosporins (CEP). However, we did not observe such a reduction with *Klebsiella pneumoniae*. Therefore, we sought to determine whether replacement of CEP by piperacillin-tazobactam might be useful in reducing sustained high rates of CEP resistance by this organism. We used a 6-month "before and after model"; during the second (intervention) period, most prescriptions of CEP were changed to piperacillin-tazobactam at the pharmacy. No additional barrier precautions were undertaken. During intervention, consumption of ceftazidime decreased from 17.73 to 1.14 defined daily doses (DDD) per 1,000 patient-days ($P < 0.0001$), whereas that of piperacillin-tazobactam increased from 0 to 30.57 DDD per 1,000 patient-days ($P < 0.0001$). The levels of resistance to CEP by *K. pneumoniae* and *P. mirabilis* decreased from 68.4 and 57.9% to 37.5 and 29.4%, respectively ($P < 0.05$). We conclude that replacement of ceftazidime by piperacillin-tazobactam might be a suitable strategy to decrease endemic CEP resistance by *K. pneumoniae* and *P. mirabilis*, even where there are high bacterial resistance rates and irrespective of any additional precautions for controlling nosocomial infection.

Nosocomial infection by multiresistant organisms is a worrisome problem worldwide, leading to increased morbidity, length of hospital stay, mortality, and health care costs (2, 6, 15, 18). Therefore, several strategies have been developed in the hope of limiting the emergence of bacterial resistance, such as formulary replacement or restriction (10), introduction of order form (8), healthcare provider education and feedback activities (7), and prescription approval requirements by an infectious diseases physician (9).

Bantar et al. (3) published alarming rates of bacterial resistance in a surveillance study involving a number of Argentinean healthcare centers and noted high rates of nosocomial infection (J. L. Bustos et al., Letter, Infect. Control Hosp. Epidemiol. **22:**264-265, 2001). More recently, we reported results from a hospital-wide intervention program carried out to optimize quality of antibiotic use within hospital. In that study, we observed a significant reduction of ceftriaxone resistance by *Proteus mirabilis* and *Enterobacter cloacae* associated with an increase in use of cefepime, in parallel with a decrease in the consumption of broad-spectrum cephalosporins (CEP). However, we did not observe a similar reduction with *Klebsiella pneumoniae* (2). Other authors have described a reduction in the rates of multiresistant *K. pneumoniae* after the replacement of CEP with piperacillin-tazobactam (9, 14, 15, 18). These interventions were promoted in response to nosocomial outbreaks and not by the problem observed in most Argentinean hospitals where such infections are endemic (2, 3). Furthermore, additional actions, such as the enhancement of barrier precautions or education, were concomitantly introduced in most of these studies (14, 15). Therefore, we sought to determine whether sustained replacement of CEP by piperacillin-tazobactam might be useful for reducing the resistance of endemic nosocomial bacteria, especially *K. pneumoniae*, in the setting of high baseline rates and irrespective of any additional infection control precautions.

MATERIALS AND METHODS

Setting. The Hospital San Martín is a 250-bed public teaching hospital for adult patients. It is located in Paraná, Argentina, a city of about 350,000 inhabitants. The hospital has a 10-bed intensive care unit and several surgical wards (including orthopedic, abdominal, thoracic, gynecological, and neurological wards), but it lacks facilities for solid organ or bone marrow transplantation and cardiac surgery.

Study design. This was a "before-and-after" study and received approval of the pertinent institutional Committee. The first period (baseline) was developed during the last 6 months of 2002. In this phase, restrictions were not imposed either to antibiotic prescribing practice or the pharmacy formulary (except for piperacillin-tazobactam and cefepime, which were not available during this period). However, an antibiotic order form was required for procuring antibiotics from pharmacy. In addition, an infectious disease physician and a clinical microbiologist assessed every antibiotic prescription for properness, and bedside discussion with attending physicians was carried out when necessary. The second period (intervention) was developed during the first 6 months of 2003 and was

* Corresponding authors. Mailing address for C. Bantar: Colón 128, 3100 Paraná, Entre Ríos. Phone: (54343)4310783. Fax: (54343) 4310783. E-mail: cbantar@arnet.com.ar. Mailing address for M. E. Oliva: Gualeguaychú 882, 3100 Paraná, Entre Ríos. Phone: (54343)4310783. Fax: (54343) 4310714. E-mail: caemi@arnet.com.ar.

TABLE 1. Variations of intravenous antibiotic consumption during a before-and-after intervention trial that replaced CEP with piperacillin-tazobactam

Antibiotic	Consumption (DDD/1,000 patient-days)[a]		P^b
	Period 1 (baseline)	Period 2 (intervention)	
Amikacin	20.91	17.64	NS
Aminopenicillin-sulbactam	28.74	15.58	0.03
Carbapenem	1.91	2.49	NS
Ceftazidime	17.73	1.14	<0.0001
Ceftriaxone	12.67	5.67	NS
Cephalotin	30.98	32.91	NS
Ciprofloxacin	11.13	22.7	NS
Clarithromycin	2.42	1.17	NS
Clindamycin	18.27	22.75	NS
Gentamicin	26.06	35.93	NS
Metronidazole	10.08	12.53	NS
Piperacillin-tazobactam	0	30.57	<0.0001
Vancomycin	8.35	9.83	NS
Total	193.8	210.91	NS

[a] See study design in the text for details.
[b] As determined by chi-square test for period 1 versus period 2. Differences between periods were analyzed by comparison of consumption of every drug with respect to the total antibiotic consumption (i.e., the variation in the relative consumption). NS, not significant.

TABLE 2. Characteristics of infections for which antibiotic was ordered during a before-and-after intervention trial that replaced CEP with piperacillin-tazobactam

Characteristic of infection	Frequency (%)[a]		P^b
	Period 1 (baseline [n = 535])	Period 2 (intervention [n = 396])	
Site			
Abdomen	17	14.6	NS
Bone	5.2	3.0	NS
Central nervous system	3.0	2.5	NS
Catheter	4.5	3.0	NS
Lung	42.6	46.5	NS
Skin and soft tissue	11.8	12.6	NS
Urinary tract	9.5	13.1	NS
Others	3.8	1.7	NS
Unknown	2.6	3.0	NS
Origin			
Community	66.4	64.9	NS
Hospital	33.6	35.1	NS
Severity			
Low	3.6	4.3	NS
Moderate	53.6	51.3	NS
High	42.9	44.4	NS
Therapy directed by culture	60.9	44.9	<0.0001

[a] See study design in the text for details.
[b] As determined by chi-square test for period 1 versus period 2. NS, not significant.

like the first period, but most prescriptions of CEP (except ceftriaxone for central nervous system infections) were changed to piperacillin-tazobactam at the pharmacy.

To evaluate the impact of the antimicrobial formulary intervention, no specific actions to control and prevent nosocomial infections, beyond the standard precautions that were being undertaken before the study was begun, were introduced by the pertinent committee during the 12 months of the study.

Data collection. Consumption of antibiotics was recorded as total grams of the drug on a homemade computerized system developed by a specialized analyst from our hospital (M. Saúl, SOUFARMA) (C. Bantar, B. Sartori, E. Vesco, M. Saúl, and G. Morera, Abstr. 101st Gen. Meet. Am. Soc. Microbiol., abstr. A-69, 2001) and then converted to defined daily dose (DDD) per 1,000 patient-days in accordance with the World Health Organization recommendation (11). Only the expenditure of drugs to be given intravenously was analyzed. Antibiotic consumption associated with surgical prophylaxis was excluded.

Bacterial resistance rates were recorded and analyzed by using a previously described homemade computerized system (SIR) developed by one of the authors (C.B.) (3). Briefly, every antibiogram result corresponding to a hospitalized patient was assessed for clinical significance and properness of specimen collection by a team composed of six physicians. Subsequently, a clinical microbiologist entered the suitable data into the software. To calculate bacterial resistance rates, the SIR system automatically eliminates multiple strains from the same patient if they display identical antibiogram and if they are recovered within a 6-month period. Susceptibility testing was carried out by the disk diffusion method according to NCCLS guidelines, including the interpretative breakpoint criteria (13). Because our laboratory belongs to the WHONET-Argentina Collaborative Group, presumptive presence of extended-spectrum β-lactamase (ESBL) was routinely screened by the double-disk diffusion test with clavulanic acid, ceftriaxone, and ceftazidime (13). Previous experiences comparing similar periods from 1999 to 2000 suggest that significant seasonal variations should not be expected to occur for any phenotype of resistance included in the present study (2, 3).

The antibiotic order form required the physician to state the certainty of infection diagnosis, as well as the most relevant epidemiological data. The infectious disease physician completed a unique form with the same data as the antimicrobial order form. The data were finally recorded and analyzed by using EpiInfo software (v. 6.0; Centers for Disease Control and Prevention, Atlanta, Ga.). The density of nosocomial infection was estimated as described previously (Bustos et al., letter). The data for number of patient admissions and discharges, number of patient days, mean length of hospital stay, and crude mortality were obtained from the Department of Statistics.

Statistics. Rates were analyzed by comparison of proportions with the chi-square or Fisher exact tests by using the EpiInfo statistical package. Nonparametric continuous variables were analyzed by comparison of means with the rank sum two-sample test (Mann-Whitney) on the software Statistix for Windows (v2.0; Analytical Software Co.). A P value of ≤ 0.05 was considered significant.

RESULTS

Antibiotic consumption. Intravenous antibiotic consumption during baseline and intervention periods is shown in Table 1. The numbers of patient-days in periods 1 and 2 were 36,550 and 33,847, respectively. Antibiotics showing significant variation in consumption from period 1 to period 2, as estimated by their relative contribution to the total consumption within the corresponding period, were aminopenicillin-sulbactam (decrease), ceftazidime (decrease), and piperacillin-tazobactam (increase). Furthermore, a doubling of ciprofloxacin consumption was observed from period 1 to period 2, but statistical significance was not reached.

Prescribing practice. In all, 535 and 396 successive unique antimicrobial order forms (i.e., corresponding to one patient each) were analyzed during periods 1 and 2, respectively. Antibiotics to be given orally were also included in this analysis. Table 2 shows the characteristics of infections for which antibiotic was ordered, such as site, origin and severity of infection, and therapy directed by culture. A higher frequency of therapy directed by culture was observed in period 1 than in period 2. The remaining characteristics were similar in both periods.

Nosocomial infection, crude mortality rate, and length of hospital stay. The nosocomial infection rate was assessed immediately before the baseline period (May 2002), at the end of

TABLE 3. Variations in bacterial resistance rates during a before-and-after intervention trial that replaced CEP with piperacillin-tazobactam

Organism/phenotypic resistance[a]	Resistance rate (%)[b]		P[c]
	Period 1 (baseline)	Period 2 (intervention)	
E. coli/CEP	11.5 (157)	8.3 (96)	NS
K. pneumoniae/CEP	68.4 (38)	37.5 (40)	0.012
P. mirabilis/CEP	57.9 (38)	29.4 (51)	0.013
P. aeruginosa/CEP	5.7 (35)	6.2 (32)	NS
P. aeruginosa/TZP	11.4 (35)	6.2 (32)	NS
Acinetobacter species/TZP	21.7 (23)	23.1 (26)	NS
S. aureus/MET	35.56 (107)	36.8 (68)	NS

[a] TZP, piperacillin-tazobactam; MET, methicillin.
[b] See program design in the text for details. Values in parentheses indicate the total number of strains.
[c] That is, for period 1 versus period 2. NS, not significant.

this phase (January 2003, beginning of intervention), and at the end of the intervention period (June 2003). The respective densities of incidence (number per 1,000 patient-days) were 3.0, 6.5 and 4.0. The mean crude mortality rates (expressed as the number of deaths per 1,000 patient-days ± the standard deviation) were 9.95 ± 1.97 and 8.84 ± 1.38 for periods 1 and 2, respectively ($P > 0.05$). The corresponding mean length of hospital stay was 9.33 ± 1.03 and 8.83 ± 0.75 days ($P > 0.05$).

Variation of bacterial resistance. In order to evaluate the impact of the formulary intervention on bacterial resistance, we selected certain worrisome multiresistant species detected in previous studies, such as CEP-resistant *Escherichia coli*, *K. pneumoniae*, *P. mirabilis*, and *Pseudomonas aeruginosa*, as well as methicillin-resistant *Staphylococcus aureus*. In addition, two phenotypes were selected to assess the impact of the increase of piperacillin-tazobactam use (i.e., *P. aeruginosa* and *Acinetobacter* species resistant to piperacillin-tazobactam). To date, vancomycin-resistant enterococcus has never been isolated in our hospital; thus, this organism was not included in the analysis. The data are summarized in Table 3. No variation was found between periods in resistance to CEP by *E. coli*. In contrast, significant decrease of this kind of resistance was observed with *K. pneumoniae* and *P. mirabilis*. Changes were not observed either in the resistance rates to piperacillin-tazobactam by *P. aeruginosa* and *Acinetobacter* species or in the frequency of methicillin-resistant *S. aureus*.

DISCUSSION

The widespread presence of resistant bacteria among hospitals has led to the common practice of using broad-spectrum antimicrobial coverage for presumed infections in hospitalized patients, with CEP being the most frequently used agents in this setting. Concomitant with the increased use of these drugs has been the emergence of extended-spectrum ESBL-producing *K. pneumoniae* (12, 17). Recently, evidence has accumulated that decreasing the use of CEP may be effective in controlling nosocomial outbreaks provoked by these organisms (9, 14, 15, 18).

We described previously a strategy to control bacterial resistance by positing the increased use of cefepime in parallel with a reduction in the consumption of CEP within our hospital. Although we observed a significant sustained reduction in ceftriaxone-resistant *P. mirabilis* over time associated with these variations in antibiotic consumption, the rates of *K. pneumoniae* resistant to CEP remained high (2). In the present study, the frequency of this organism decreased by 45% after complete replacement of CEP, especially ceftazidime, with piperacillin-tazobactam, even though the periods of observation were relatively short and the study relied on convenience samples that were submitted for clinical diagnosis and not active surveillance. We were unable to assess clonality between isolates; thus, the likelihood of clone replacement during the study cannot be ruled out. In any event, antibiotic use measures seem to be particularly important for control of multidrug-resistant *K. pneumoniae*, whether emergence is clonal or polyclonal, as demonstrated by Patterson et al. (14). Indeed, these authors and others used similar strategy to control nosocomial outbreaks by multiresistant *K. pneumoniae* (14, 15, 18). However, several major differences between our experience and that of these earlier studies should be pointed out: (i) the interventions described above were prompted by a nosocomial outbreak rather than an endemic problem (i.e., our situation); (ii) apart from one study (18), all of these earlier studies included barrier precautions or education as additional interventions, in contrast to our experience, which included only formulary intervention as a variable between periods; (iii) the baseline rate of *K. pneumoniae* resistant to CEP was far higher in our hospital than in the experiences described above; and (iv) apart from CEP or piperacillin-tazobactam, the studies described above did not assess consumption of the vast diversity of other antibiotics commonly used during the intervention phase, which might also be associated with variations in resistance rates.

Because our study was a before-and-after model, we sought to rule out any bias provoked by changes in certain variables able to impact on the CEP resistance by *K. pneumoniae*, such as origin, source and severity of infection, consumption of the various antibiotics used in the hospital, and the length of hospital stay. Indeed, relationships between patient-specific variables (i.e., duration of hospital stay and primary diagnosis) and decreased susceptibility of gram-negative pathogens have been recently described (4). It should be noted that rate of therapy directed by culture was less frequent during the second period, and we did not find any reason for this finding. Although this may constitute a potential bias leading to underestimation of the number of resistant organisms during this period, the fact that all of the other variables, including the relative distribution of the different bacterial species, remained unchanged, leads us to hypothesize that this was a chance phenomenon and that its contribution to a bias would be unlikely.

On the other hand, we observed pronounced variations in consumption of ceftazidime, piperacillin-tazobactam and to a lesser extent, aminopenicillin-sulbactam. We previously demonstrated that variations of aminopenicillin/sulbactam consumption did not influence CEP resistance by *K. pneumoniae* and *P. mirabilis* (2). Therefore, it might be inferred that replacement of ceftazidime by piperacillin-tazobactam was responsible for the variations of resistance by these organisms observed in the present study. Although the likelihood of a temporal association cannot be ruled out, we were aware of additional indirect evidence of the association between the use

of CEP and the increase of this kind of resistance in our hospital. For instance, because of the pronounced economic crisis that occurred in our country at the end of 2001, cefepime was completely abandoned in our center and ceftazidime and ceftriaxone usage became more frequent during 2002. Concomitantly, the respective CEP resistance rates by *K. pneumoniae* and *P. mirabilis* increased from 42 and 27% at the end of our previous experience (i.e., January to June 2001) (2) to 68.4 and 57.9% at the baseline period of the present study (i.e., July to December, 2002) (Table 1).

The knowledge of the β-lactamases involved in this kind of resistance may shed light on the decrease in resistance rates exerted by our formulary intervention. In our country, CEP resistance by *K. pneumoniae* and *P. mirabilis* proved to be mainly mediated by the ESBL CTX-M-2 type (16), and in vitro resistance by these strains is displayed more frequently against CEP and cefepime than against piperacillin-tazobactam. In fact, all strains of *K. pneumoniae* with the ESBL phenotype recovered in 1997 at our hospital were proven to possess ESBL CTX-M-2 type at a surprisingly high frequency (>70%), as shown by a collaborative surveillance study carried out in our country (M. Galas, M. Rapoport, F. Pasterán, R Melano, A. Petroni, P. Ceriana, A. Rossi, et al., Abstr. 39th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 1474, 1999). J. M. Casellas and two of us (C.B. and F.S.) (5) recently published a multicenter study on the in vitro comparative activity of piperacillin-tazobactam against selected strains recovered from hospitalized patients in Argentina. That study included several isolates from our hospital, and the resistance rates to ceftriaxone, ceftazidime, cefepime, and piperacillin-tazobactam by *K. pneumoniae* strains with ESBL phenotype were 100, 93, 70, and 32%, respectively, whereas the respective values for *P. mirabilis* were 100, 37.5, 50, and 0%. This phenomenon may explain why we observed a reduction of ceftriaxone-resistant *K. pneumoniae* by replacing CEP with piperacillin-tazobactam, as we did in the present study, but not with cefepime, as we did in our previous experience (2). It should be noted that these findings might not be always extrapolated to other settings, since susceptibility of *K. pneumoniae* to piperacillin-tazobactam may vary in accordance with the type of ESBL involved, as suggested recently by Babini et al. (1). It is of interest that we did not observe any significant variation in the rates of *E. coli* strains with an ESBL phenotype, either during the previous experience (2) or during the present one. This may be attributable to the lower prevalence of ESBL in *E. coli*.

The resistant phenotypes we selected to monitor the impact of increasing piperacillin-tazobactam consumption (i.e., *P. aeruginosa* and *Acinetobacter* spp. resistant to this drug) did not vary after intervention. This finding is conflicting with that of Landman et al. (9), who observed increase in cefotaxime resistance by *Acinetobacter* species after the addition of piperacillin-tazobactam to the hospital antibiotic formulary. However, the results might not be comparable, since these authors demonstrated a significant reduction in the consumption of imipenem (an antibiotic commonly active against *Acinetobacter* spp.), and this feature was not observed in our experience.

We conclude that the replacement of ceftazidime by piperacillin-tazobactam might be a suitable strategy to decrease endemic CEP resistance by *K. pneumoniae* and *P. mirabilis*, even in situations where there are high bacterial resistance rates and irrespective of any additional precautions for controlling nosocomial infection.

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